least one salt to an airway surface of the subject in an amount effective to increase the volume of liquid on the airway surface;

wherein said at least one salt comprises a combination of different salts;

and wherein said combination of different salts have either *(i)* a same anion or *(ii)* a same cation.

Remarks

Applicant appreciates the thorough examination of the present application as evidenced by the Official Action (the Action) dated November 13, 2002. Claims 1, 14-21, and 31-51 are pending in the present application, and Claims 1, 14, 15, 20, 31-44, 50, and 51 are under examination. Claims 1, 15, 20, 31-36, 42-44, and 50-51 stand rejected under 35 U.S.C. § 102(e). Claims 1, 14, 15, 20, 31-44, and 50-51 stand rejected under 35 U.S.C. § 103(a). Applicant has amended the specification in order to correct a typographical error. Applicant has amended Claim 37. Support for amended Claim 37 can be found in the specification at page 4, lines 4-23, and in amended Claim 1 and new Claims 37-39 as presented in the Preliminary Amendment filed March 1, 2002. The concerns raised by the Examiner are addressed below as set forth in the Action.

I. **Claim 37.**

Claim 37 stands rejected as obvious. Applicant respectfully disagrees with this rejection for the reasons set forth below. In addition, Claim 37 has been rewritten in independent form and amended to incorporate both species of Claims 38 and 39 to more particularly point out this embodiment of the invention. In addition to the points raised below, it is respectfully submitted that nothing in the cited references suggests administering a combination of

salts sharing a common anion or cation, particularly given the different under theory underlying the methods of the cited reference and the instant invention.

II. Claim Rejections Under 35 U.S.C. § 102

Claims 1, 15, 20, 31-36, 42-44, and 50-51 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,863,563 to Scheele (Scheele). More specifically, the Action asserts that "Scheele teaches a method of treating a patient with cystic fibrosis comprising causing the patient to inhale a composition comprising potassium bicarbonate. See, particularly, claims 1, 4, and 6." Action, page 2. Applicant respectfully disagrees with this assertion.

"Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer Inc. v. Articulate Systems Inc.* 57 USPQ2d 1057, 1061 (Fed. Cir. 2000) (*relying on Electro Med. Sys. S.A. v. Cooper Life Scis.,* 32 USPQ2d 1017, 1019 (Fed Cir. 1994). A finding of anticipation further requires that there must be **no difference** between the claimed invention and the disclosure of the cited reference as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991) (emphasis added). Additionally, the cited prior art reference must be enabling, thereby placing the allegedly disclosed matter in the possession of the public. *In re Brown*, 329 F.2d 1006, 1011, 141 U.S.P.Q. 245, 249 (C.C.P.A. 1964). Thus, the prior art reference must adequately describe the claimed invention so that a person of ordinary skill in the art could make and use the invention.

Applicant respectfully submits that Scheele does not disclose all the recitations of the claims of the present invention and does not adequately describe the claimed invention so that a person of ordinary skill in the art could make and use the invention.

The present invention relates to a method for treating chronic obstructive pulmonary disease, comprising administering at least one osmotically active compound to an airway surface in an amount effective to increase the volume of liquid on the airway surface wherein the at least one osmotically active compound comprises at least one salt, as recited in Claim 1. In contrast, Scheele relates to a method for treating the symptoms of a pulmonary condition involving **insufficient secretion of surfactant by type II alveolar cells**, said insufficiency being attributable to abnormally low pH of the aqueous film bathing the alveolar luminal surface of said cells, said method comprising causing a patient suspected of having said pulmonary condition to inhale an amount of a **pH-raising buffer** effective to alleviate said symptoms, wherein (1) the buffer is provided to the patient in the form of a powder, and (2) said pulmonary condition is selected from the group consisting of, among other things, cystic fibrosis, as recited in Claim 1 of Scheele. Applicant submits that Scheele does not recite a method for treating chronic obstructive pulmonary disease, comprising among other things, administering at least one **osmotically active compound to an airway surface of the subject in an amount effective to increase the volume of liquid on the airway surface**. The use of osmolytes to alter the volume of liquid on the airway surface as disclosed in the present invention is not equivalent to the administration of a pH-raising buffer to increase the rate of surfactant by type II alveolar cells as proposed by Scheele.

While not wishing to be bound to any particular theory, Applicant notes that the relationship between volume depletion on airway surfaces and mechanisms for mucus transport play a role in the understanding of cystic fibrosis (CF) pathogenesis. Airway surface liquid (ASL) consists of at least two layers: a mucus layer and a perciliary liquid layer. The mucus layer comprises high molecular weight, heavily glycosylated macromolecules that, among other things, bind and trap inhaled particles for clearance from the lungs. The perciliary liquid layer (PCL), previously described in the literature

as the "sol" layer, is a mucus-free zone at the cell surface that approximates the height of the outstretched cilia of the lung epithelial cells. Under normal conditions, the PCL provides a low-viscosity solution in which the cilia can beat rapidly to remove the trapped particles in the mucus layer (mucociliary clearance) and, among other things, shields the epithelial cell surface from the overlying mucus layer. The loss of ASL volume can account for the severe phenotype of CF lung disease. The loss of volume from the mucus layer can attribute to the characteristic thickened mucus. Loss of volume from the PCL layer removes the liquid in which the cilia can extend and beat, and thus, can inhibit mucociliary clearance. Loss of volume from the PCL can also compromise the PCL's lubricant function, allowing the mucus layer to adhere to cell surfaces and inhibit cough clearance. The present invention is directed to methods for treating chronic obstructive pulmonary disease, including cystic fibrosis, comprising administering at least one osmotically active compound to an airway surface in an amount effective to **increase the volume of liquid on the airway surface** wherein the at least one osmotically active compound comprises at least one salt, as recited in Claim 1.

At column 1, line 51 through column 2, line 15, Scheele proposes an invention based on the alleged discovery that the pulmonary dysfunction characteristic of certain disease states is attributable to the inhibition of secretion of surfactant and other secretory molecules normally produced by type II alveolar cells. Scheele further proposes that this inhibition of secretion is believed to be caused by the uncoupling of endocytosis and exocytosis in these cells, as a result of an abnormally low pH at the apical surface, in the alveolar microenvironment. Scheele also proposes that abnormally low pH of the aqueous fluid bathing the apical surface of type II alveolar cells causes a generalized decrease in the normal rate of membrane trafficking within the type II cells. Specifically, Scheele proposes that an abnormally low pH in the vicinity of the type II alveolar cells causes a defect in the intracellular recycling of exocytic membranes at the apical plasma membrane, a process that

normally occurs during apical endocytosis in these cells. Scheele alleges that impaired endocytosis results in a generalized defect in the secretory process, including secondary effects which involve a significant decrease in the level of membranes available for exocytosis. Scheele further alleges that impairment of exocytosis inhibits secretion by type II alveolar cells, in particular secretion of surfactant and other molecules important for pulmonary function. Scheele asserts that this decrease in secretion of surfactant, in turn, causes an increase in surface tension of the aqueous film bathing the lumenal aspect of the alveolar space, a decrease in the elastic properties of pulmonary tissue, a concomitant decrease in the rate of gas exchange within the alveolus, and an overall decrease in pulmonary function. Scheele concludes that as a result, the patient develops a pulmonary disease syndrome, including hampered breathing and inefficient gas exchange.

Scheele then proposes a method of treatment that involves causing a patient to inhale an amount of a pH-raising buffer effective to raise the pH of the aqueous fluid in the lumenal microenvironment of the type II alveolar cells, thereby inducing an increased level of vesicular membrane trafficking and a concomitant increase in the rate of surfactant secretion by type II alveolar cells. According to Scheele, this results in alleviation of the symptoms of the pulmonary condition, and a lessening of pulmonary dysfunction.

Applicant submits that employing an agent to raise pH, which in turn, may lead to an increase in the rate of surfactant secretion by type II alveolar cells and employing an agent that is osmotically active, i.e., membrane-impermeable or essentially non-absorbable on airway or pulmonary epithelial surfaces (See Present Application, page 4, lines 4-11) to increase the volume of liquid on the airway surface, clearly relate to distinct processes. Thus, the use of osmolytes to alter the volume of liquid on the airway surface as disclosed by the present invention is not equivalent to the administration of a pH-raising buffer to increase the rate of surfactant secretion by type II alveolar cells as proposed by Scheele.

Moreover, Applicant further submits that Scheele fails to provide teachings that would enable a person of ordinary skill in the art to make and use the present invention. Applicant submits that one of ordinary skill in the art would not rely upon the proposals of Scheele directed toward using a pH-buffer effective to raise the pH of the aqueous fluid in the luminal microenvironment of the type II alveolar cells for the purpose of increasing surfactant secretion by type II alveolar (See Col. 2, lines 23-30) in order to arrive at a method comprising, among other things, administering at least one osmotically active compound to an airway surface of the subject in an amount effective to increase the volume of liquid on the airway surface. As noted above, the method disclosed in the present application and the method proposed by Scheele clearly relate to distinct processes.

Accordingly, Applicant respectfully submits that Claims 1, 5, 20, 31-36, 42-44, and 50-51 are not unpatentable under 35 U.S.C. § 102(e) as being anticipated by Scheele and request that this rejection be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 103

Claims 1, 14, 15, 20, 31-44, and 50-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Scheele in view of U.S. Patent No. 5,162,348 to Glass (Glass). More specifically, the Action asserts that " it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to employ more than one of the known salts disclosed by Scheele in the therapeutical composition, or treating the patient with a bronchodilator before administering the instant composition." Action, page 3. Applicant respectfully disagrees with this assertion.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim recitations. *See In re Wilson* , 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion

or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

Moreover, the cited references, when combined, must teach or suggest *all* the recitations of the claims, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. §2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. §2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The Court of Appeals for the Federal Circuit has further stated that, to support combining or modifying references, there must be **particular** evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

As stated above, Scheele fails to teach or suggest all the claim recitations of the present invention directed to a method for treating chronic obstructive pulmonary disease, comprising administering at least one osmotically active compound to an airway surface in an amount effective to increase the volume of liquid on the airway surface wherein the at least one osmotically active compound comprises at least one salt, as recited in Claim 1. Scheele fails to teach or suggest all the claim recitations of the present invention directed to a method for treating chronic obstructive pulmonary disease, comprising administering, among other things, at least one

osmotically active compound that comprises at least one salt wherein the at least one salt comprises a combination of different salts having a (i) same anion or (ii) same cation, as recited in amended Claim 37. The Action acknowledges that "Scheele does not teach expressly the employment of combination salts, or the further employment of a bronchodilator in the composition." Action, page 3. Glass is employed to "teach that bronchodilators are well known to be useful for treating cystic fibrosis." Action, page 3. However, Glass does not supply **all** the missing recitations such as those directed to the use of osmolytes to alter the volume of liquid on the airway surface as disclosed by the claims of the present invention.

Applicant further notes that there is no suggestion or motivation to combine Scheele and Glass, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. The method disclosed in the present application and the method proposed by Scheele clearly relate to distinct processes, and Glass does not supply all the missing recitations— neither through disclosure nor suggestion. As such, the cited references, alone or in combination, fail to provide a reasonable expectation of success of arriving at the present invention.

Where Scheele, alone or in combination with Glass, fails to disclose all the claim recitations of the present invention, fails to suggest the modification of the references or the combination of reference teachings in order to arrive at the claimed invention and lastly, fails to provide a reasonable expectation of success, the Examiner has failed to establish a *prima facie* case of obviousness.

Accordingly, Applicant respectfully submits that Claim 1, 14, 15, 20, 31-44, and 50-51 are not unpatentable under 35 U.S.C. § 103(a) in view of Scheele in further view of U.S. Patent No. 5,162, 348 to Glass and requests that this rejection be withdrawn.

IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,

Kenneth D. Sibley
Registration No. 31,665

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on February 13, 2003.

Vickie Diane Prior
Date of Signature: February 13, 2003

Version With Markings To Show Changes Made

In the Specification:

On page 1, please replace the paragraph under "**STATEMENT OF FEDERAL SUPPORT**" with the following paragraph.

-- This invention was made with government support under Grant No. HL34322 **[HL51818]** from the National Institutes of Health. The United States Government has certain rights in this invention. --

In the Claims:

Please amend Claim 37 as follows.

37. (Amended) **[A method according to claim 1,]** A method for treating chronic obstructive pulmonary disease in a subject in need of such treatment, comprising administering at least one salt to an airway surface of the subject in an amount effective to increase the volume of liquid on the airway surface;

wherein said at least one salt comprises a combination of different salts;

and wherein said combination of different salts have either *(i)* a same anion or *(ii)* a same cation.